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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 30 29

Application Number: 08/758,033
Filing Date: November 27, 1996
Appellant(s): Clayman, G.L.

Steven L. Highlander
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 16, 1999, paper # 27.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

Art Unit: 1632

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment filed November 16, 1999, paper # 24 has been entered. Claims 33-35, 69-72, 104-107, 133-136, 140, 141, 144 and 145 are canceled.

Appellants petition filed November 16, 1999, paper # 25, requesting the entry of the amendment after final filed September 13, 1999, paper # 19, is denied. Appellants argue that the amendment which inserts the term "catheterization" into claim 109 does not raise a new consideration. Appellants argue that delivery by a catheter was previously present in claim 122. However, appellants did not cancel claim 122 when they requested amendment to claim 109. This raised a new rejection under 35 USC § 112, second paragraph. Therefore, the petition is denied and the amendment filed September 13, 1999, paper # 19 remains unentered.

Art Unit: 1632

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

A. The issue of whether claims 33-35, 69-72, 104-107, 133-136, 140, 141, 144 and 145 are enabled under 35 USC § 112, first paragraph is moot in view of the entry of the amendment filed November 16, 1999, paper #24 which canceled these claims.

B. The issue of whether claims 1-14, 16-20, 26-37, 74-77, 80-108, 140 and 144 are indefinite under 35 USC § 112, second paragraph is moot in view of the entry of the amendment filed November 16, 1999, paper # 24 which canceled claims 140 and 144.

C. The issue remains as to whether claims 38-40 and 42-68, 73, 109-113 and 115-132 and 137 are rejected under 35 USC § 103, as being obvious over Liu et al. or Wills et al. in view of Zhang et al. or Bramwell et al.

The prior rejection of claims 41 and 114 under 35 USC § 103, as being obvious over Liu et al. or Wills et al. in view of Zhang et al. or Bramwell is withdrawn.

Art Unit: 1632

D. The issue remains as to whether claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 are rejected under 35 USC § 103, as being obvious over Cajot et al. taken with Wills et al. or Liu et al., in view of Zhang et al. or Bramwell.

The prior rejection of claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 under 35 USC § 103 as being obvious over Katayose et al. or Srivastava et al. is withdrawn in view of appellants filing of a Declaration under 37 CFR § 1.131 on November 16, 1999, paper # 25.

(7) *Grouping of Claims*

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because appellants fail to particularly point out why all of the pending claims stand or fall separately. Appellants argue in Section IX.C.iv why various groups of claims do not stand or fall together based on the absence of teachings in the prior art. For the reasons set forth in Section IX.C.iv, the groupings of the claims stand or fall together.

Therefore:

Claims 2, 39, 76, and 111 directed to inhibiting the growth of a carcinoma, glioma, sarcoma, or melanoma stand or fall together.

Claims 10 and 121 directed to humans stand or fall together.

Claim 12 directed to two or more administrations of p53 viral vectors stands or falls separately.

Art Unit: 1632

Claim 17 directed to continuous perfusion of a natural or artificial body cavity stands or falls separately.

Claims 28, 29, 31, 61, 62, 63, 65, 67, 96, 100, 102, 125-129 and 131 directed to various combination therapies stand or fall together.

All other pending claims stand or fall together.

(8) *Claims Appealed*

A substantially correct copy of appealed claims appears on pages 28-38 of the Appendix to the appellant's brief. The minor errors are as follows: Claims 33-35, 69-72, 104-107, 133-136, 140, 141, 144 and 145 are listed in the appendix, but are not pending claims. Note, appellants have indicated these claims as canceled in parenthesis.

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

- ✓ Liu et al. "Growth Suppression of Human Head and Neck Cancer Cells by the Introduction of a Wild-Type p53 Gene via a Recombinant Adenovirus." Cancer Research, vol. 54 (July 15, 1994), pp. 3662-3667.

Art Unit: 1632

✓ Wills et al. "Development and Characterization of Recombinant Adenovirus Encoding Human p53 for Gene Therapy of Cancer." Human Gene Therapy, vol. 5 (September 1994), pp. 1079-1088.

✓ Zhang et al. "Gene Therapy Strategies for Cancer." Exp. Opin. Invest. Drugs, vol. 4, no. 6 (June 1995), pp. 487-514.

✓ Bramwell, V. "The Role of Chemotherapy in Multimodality Therapy." The Canadian Journal of Surgery, Vol. 31, No. 5 (September 1988), pp. 390-396.

Cajot et al. "Growth Suppression Mediated by Transfection of p53 in Hut292DM Human Lung Cancer Cells Expressing Endogenous Wild-Type p53 Protein." Cancer Research, vol. 52, no.24 (1992), pp. 6956-6960.

Katayose et al. "Cytotoxic Effects of Adenovirus-mediated Wild-Type p53 Protein Expression in Normal and Tumor Mammary Epithelial Cells." Clinical Cancer Research, vol. 1 (August 1995), pp. 889-897.

Art Unit: 1632

Srivastava et al. "Recombinant Adenovirus Vector Expressing Wild-Type p53 is a Potent Inhibitor of Prostate Cancer Cell Proliferation." *Urology*, vol. 46, no6 (1995), pp. 843-848.

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Claims 38-40, 42-68, 73, 109-113 and 115-132 and 137 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) in view of Zhang et al. or Bramwell.

Liu et al. (Cancer Research, Vol. 54 (1994)) taught the growth suppression of squamous cell carcinoma of human head and neck cancer (SCCHN) established *in vivo* in nude mice following the administration of adenoviral vectors encoding wild-type p53. At page 3666, column 2, Liu et al. state that the regression in cancer burden in nude mice was at least 60 times more than in the experimental controls. The adenoviral vector taught by Liu et al. lacked a portion of the E1 region and contained a CMV promoter (see second to last paragraph, page 3662). Liu et al. did not teach that expression of wild-type p53 by SCCHN cancer cells made the cancer cells susceptible to radiation therapy.

However, also at the time the claimed invention was made, Wills et al. (Human Gene Therapy, Vol. 5 (1994)) taught inhibition of tumor proliferation and tumorigenicity following a

Art Unit: 1632

single injection of recombinant adenoviral vectors encoding wild-type p53 protein into carcinoma cell lines grown *in vitro* or introduced established tumor *in vivo* in a nude mouse. The adenoviral vector taught by Wills et al. contained either an MLP or CMV promoter and lacked a portion of the E1 region (see second column, page 1080). Wills et al. additionally taught that repetitive administration of adenoviral vectors encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example). Additionally, at page 1086, column 2, Wills et al suggests that the ability to express wild-type p53 in cancer cells may increase the tumor cells susceptibility to radiation therapy or chemotherapy. Specifically, Wills et al. state:

Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may have become so due in part to the lack of wild-type p53. **By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy.**

(emphasis added). Wills et al. does not teach administration and reduction of tumor burden for treatment of squamous cell carcinoma. Wills et al. taught that replication deficient adenoviral vectors which have deletions in the E1 region can be used in the method (see materials and method section) and that the CMV promoter functioned better than the MLP promoter (see materials and method section and page 1083).

Art Unit: 1632

Each of Zhang et al. or Bramwell taught the advantage to combination therapy. Specifically, Zhang et al. reviews various treatments for cancer and concludes at page 505 that with respect to cancer therapy, combinational approaches of using gene therapy, chemotherapy, immunotherapy, radiotherapy, and surgery is the most logical and has the greatest potential for a more advanced therapy. Zhang et al. additionally discusses the use of p53 in treating cancer (see pages 493-494). Bramwell reviews various chemotherapeutic agents (such as actinomycin D and adriamycin) and discusses the benefits of combining such therapies. Bramwell also discusses combining radiotherapy with chemotherapy (see page 394) to improve inhibition of cancer.

Therefore, given the above teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of any one of Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) with that of Zhang et al. or Bramwell and treat microscopic residual cancer with adenoviral vectors encoding p53 polypeptide with a reasonable expectation of success. It would also have been obvious to one of ordinary skill in the art to combine treatment regimens of surgery, gene therapy, radiation therapy and chemotherapy as suggested by Zhang et al. Surgery, radiation therapy and chemotherapy had been practiced and combined in the art for years to inhibit cancer. Zhang et al. specifically states that it is only natural for one of skill in the art to utilize gene therapy methods with these other well known cancer treatments (see page 493, first column, last paragraph; and page 505, second column). The ordinary artisan would

Art Unit: 1632

have been motivated to combine these references because they all discuss therapeutic models for treating cancer. Additionally, each of Wills et al, Zhang et al. and Bramwell teach that multimodality therapy has advantages over a single therapy in treating cancer.

With respect to claims 109-113, 115-132 and 137 directed to continuous perfusion, the phrase "continuous perfusion" is a relative term such that a single injection into a tumor is continuous perfusion during the time the injection is being performed. Thus, both Liu et al. and Wills et al. taught continuous perfusion. Furthermore, it was well known in the art at the time of the claimed invention that the longer the vector is in contact with the cell, the greater the transduction efficiency. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perfuse the tumor site with adenovirus for periods longer than a single injection for the added benefit of achieving greater transduction efficiency. Wills et al. alludes to this in that multiple injections of adenovirus vector encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to increased tumor inhibition. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example).

Claims 91 and 122 are directed to delivery of the adenoviral vector through a catheter. Catheter is defined as "A tube passed through the body for evacuating or injecting fluids into body cavities." Taber's Cyclopedic Medical Dictionary, 1968. Stedman's Medical dictionary defines catheter as "a tubular instrument to allow passage of fluid from or into a body cavity." Thus, a needle is a catheter.

Art Unit: 1632

Claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cajot et al. taken with Wills et al. or Liu et al., in view of Zhang et al. or Bramwell.

Cajot et al. taught transfection of tumor cells which express endogenous p53 with exogenous p53 and demonstrated that these cells (Hut292DM cells) were inhibited in proliferation following transduction and expression of exogenous p53 both *in vitro* and when implanted *in vivo* (see entire article, especially abstract and pages 6956 & 6959). Cajot et al. did not teach *in vivo* transduction with a viral expression construct encoding p53.

However, at the time the claimed invention was made, Liu et al. (Cancer Research, Vol. 54 (1994)) taught the growth suppression of squamous cell carcinoma of human head and neck cancer (SCCHN) established *in vivo* in nude mice following the administration of adenoviral vectors encoding wild-type p53. At page 3666, column 2, Liu et al. state that the regression in cancer burden in nude mice was at least 60 times more than in the experimental controls. Liu et al. did not teach that expression of wild-type p53 by SCCHN cancer cells made the cancer cells susceptible to radiation therapy.

Also at the time the claimed invention was made, Wills et al. (Human Gene Therapy, Vol. 5 (1994)) taught inhibition of tumor proliferation and tumorigenicity following a single injection of recombinant adenoviral vectors encoding wild-type p53 protein into carcinoma cell

Art Unit: 1632

lines grown either *in vitro* or into established tumor *in vivo* in a nude mouse. Wills et al. additionally taught that repetitive administration of adenoviral vectors encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example). Additionally, at page 1086, column 2, Wills et al suggests that the ability to express wild-type p53 in cancer cells may increase the tumor cells susceptibility to radiation therapy or chemotherapy. Specifically, Wills et al. state:

Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may have become so due in part to the lack of wild-type p53. By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy.

Wills et al. does not teach administration and reduction of tumor burden for treatment of squamous cell carcinoma. Wills et al. taught that replication deficient adenoviral vectors which have deletions in the E1 region can be used in the method (see materials and method section) and that the CMV promoter functioned better than the MLP promoter (see materials and method section and page 1083).

Each of Zhang et al. or Bramwell taught the advantage to combination therapy. Specifically, Zhang et al. reviews various treatments for cancer and concludes at page 505 that with respect to cancer therapy, combinational approaches of using gene therapy, chemotherapy, immunotherapy, radiotherapy, and surgery is the most logical and has the

Art Unit: 1632

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Therefore, given the above teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of any one of Cajot et al., Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) with that of Zhang et al. or Bramwell and treat a tumor which comprises cells that express a functional p53 polypeptide with adenoviral vectors encoding p53 polypeptide with a reasonable expectation of success given that Cajot et al. specifically teaches that both p53 positive and p53 negative tumors can be inhibited by expression of exogenous p53. Wills et al. demonstrates that one of ordinary skill in the art would have a reasonable expectation of success for treating tumors *in vivo* because he demonstrates that the *in vitro* results of expression of p53 in various tumor cell lines correlates with the *in vivo* expression of these tumors (see page 1083-1084 and page 1085, last paragraph). It would also have been obvious to one of ordinary skill in the art to combine treatment regimens of surgery, gene therapy, radiation therapy and chemotherapy as suggested by Zhang et al. Surgery, radiation therapy and chemotherapy had been practiced and combined in the art for years to inhibit cancer. Zhang et al. specifically states that it is only natural for one of skill in the art to utilize gene

Art Unit: 1632

therapy methods with these other well known cancer treatments (see page 493, first column, last paragraph; and page 505, second column). The ordinary artisan would have been motivated to combine these references because they all discuss therapeutic models for treating cancer. Additionally, each of Wills et al, Zhang et al. and Bramwell teach that multimodality therapy has advantages over a single therapy in treating cancer.

With respect to claims 109-113, 115-132 and 137 directed to continuous perfusion, the phrase "continuous perfusion" is a relative term such that a single injection into a tumor is continuous perfusion during the time the injection is being performed. Thus, both Liu et al. and Wills et al. taught continuous perfusion. Furthermore, it was well known in the art at the time of the claimed invention that the longer the vector is in contact with the cell, the greater the transduction efficiency. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perfuse the tumor site with adenovirus for periods longer than a single injection for the added benefit of achieving greater transduction efficiency. Wills et al. alludes to this in that multiple injections of adenovirus vector encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example).

Claims 91 and 122 are directed to delivery of the adenoviral vector through a catheter. Catheter is defined as "A tube passed through the body for evacuating or injecting fluids into body cavities." Taber's Cyclopedic Medical Dictionary, 1968. Stedman's Medical dictionary

Art Unit: 1632

defines catheter as “a tubular instrument to allow passage of fluid from or into a body cavity.”

Thus, a needle is a catheter.

(11) *Response to Argument*

Pages 4-5 of the Brief give a Summary of the Argument set forth by appellants. Since the issues addressed in this section are also addressed in the argument, only the argument section has been specifically referenced.

A. The prior rejection of claims 33-35, 69-72, 104-107, 133-136, 140, 141, 144 and 145 under 35 USC § 112, first paragraph is moot in view of appellants cancellation of these claims.

B. The prior rejection of claims 1-14, 16-20, 26-37, 74-77, 80-108, 140 and 144 under 35 USC § 112, second paragraph is moot in view of the entry of the amendment filed November 16, 1999, paper # 24 which canceled claims 140 and 144.

C. 35 USC § 103

(i) Liu, Wills, Zhang and Bramwell

Claims 38-40, 42-68, 73, 109-113 and 115-132 and 137 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) in view of Zhang et al. or Bramwell.

(a) Tumor Resection Claims (38-68 and 73)

Appellants argue that none of Liu et al., Wills et al., Zhang et al. or Bramwell et al. teach treatment of microscopic residual tumors. Appellants argue that Zhang only teaches that

Art Unit: 1632

surgery may at some point in time be used in combination with gene therapy, and fails to suggest treatment of microscopic residual disease. Appellants argue that the suggestion by Zhang et al. to combine gene therapy with other well known conventional therapies, such as surgery, is so vague that it is irrelevant. Appellants suggest, that at best, Zhang in combination with Liu et al. teaches a mere exposure of the tumor for administration of the p53 gene. Appellant's arguments have been carefully considered, but are not deemed persuasive.

It is initially noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). What is well known and well established to one of ordinary skill in the art cannot be ignored when determining what the combination of disclosures suggests. Appellants appear to be arguing that surgical resection of tumors was unknown at the time of the claimed invention, but if enabled, Zhang suggests that combination of this surgical resection of tumors with gene therapy would be advantageous. However, such is not the case. Surgical resection of tumors is so well established in the art, that it is a routine procedure that has been performed on numerous tumors for numerous years. Reducing the tumor burden by surgical procedures prior to treatment with chemotherapy, or radiation therapy is very well established in the art. Once the tumor is removed, the unseen tumor which has not been removed is known in the art as microscopic residual disease or microscopic residual tumor. Reference to a basic oncology textbook provides support for this well known methodology.

Art Unit: 1632

For example, "Clinical Oncology, A Multidisciplinary Approach" provides ample evidence that treating tumors with radiation or chemotherapy following resection of the primary or secondary tumor was routine. See page 232, Figure 19.2; page 233, both columns; page 234, first column, page 235, first column, especially paragraph 4, under Combined Modalities; page 240, second column; page 242, first column under Combined Modalities; page 244 first column; and page 318, first column. Appellants claims are not directed to a tumor where surgical procedures are specifically not recommended, but recite the treatment of all tumors in general or specific tumors where surgical removal of the tumor is not only standard in the art, but in some situations is considered a must. Given that surgery was standard in the art, the ordinary artisan would have been motivated to combine the teachings of either of Liu et al. or Wills et al. as suggested by Zhang et al. (see Zhang et al., pages see pages 493-494 and 505) to treat microscopic residual cancer known to be present following surgery.

Appellants argue that Bramwell is not at all relevant to the combination of teachings. However, Bramwell is pertinent to the obviousness of claims 62, 63, 68, 129, 131 and 132.

(b) Perfusion Claims (109-132 and 137)

Appellants argue that "continuous perfusion" is well defined in the specification on page 33. Appellants argue that the examiner's interpretation of the phrase "continuous perfusion" as being broad enough to encompass a single bolus injection is improper.

Appellants accuse the examiner of providing hindsight reasoning. Finally, Appellants argue

Art Unit: 1632

that the examiner has not provided motivation to combine the various references applied.

Appellants arguments have been carefully considered, but are not deemed persuasive.

As specified above under "Grounds of Rejection", Catheter is defined as "A tube passed through the body for evacuating or injecting fluids into body cavities." Taber's Cyclopedic Medical Dictionary, 1968. Stedman's Medical dictionary defines catheter as "a tubular instrument to allow passage of fluid from or into a body cavity." Thus, a needle is a catheter. As specified in the specification at page 33, continuous perfusion includes catheterization for a time period "selected by the clinician for the particular patient and situation." This encompasses any therapeutic amount of time determined by a clinician. Since a needle is a catheter as defined in an ordinary medical dictionary, a single injection of adenoviral vectors encoding p53 as taught by Liu et al. or Wills is encompassed within the claims with the exception of claim 120. Since the "definition" of continuous perfusion provided in the specification is broad and reasonably encompasses delivery through a needle, the examiner has properly applied the art.

Appellants argue that the examiner has not provided any evidence which suggests that the longer the vector is in contact with the cell, the greater the transduction efficiency. However, as previously stated, Wills et al. specifically teaches that there is a dose dependant inhibition of tumors when infected with adenoviral vectors encoding p53 and that repetitive administration of adenoviral vectors encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth (see page 1082,

Art Unit: 1632

column 2-1083; and Figure 4). Also at page 1086, first paragraph, Wills et al. states, "The surviving animals still exhibit growing tumors, which may reflect cells not initially infected with the p53 recombinant adenovirus. **Higher or more frequent dosing schedules** may address this," (emphasis added). Thus, given the teachings of Wills et al. which directly addresses that increased dosage and frequency results in better transduction efficiencies of the tumor cells, one of ordinary skill in the art would have readily determined that longer exposure to the vector would increase transduction efficiency.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, the references themselves provide the motivation to combine, since Liu et al. and Wills et al. are both directed to treating tumors with p53 adenoviruses and Zhang et al. specifically teaches combining p53 gene therapy treatment with other well known cancer treatment methods such as surgery, radiation therapy, chemotherapy and immunotherapy (see pages 1083-1084; page 1085, last paragraph; and page 505 second column, respectively). Zhang et al. explicitly directs one of ordinary skill in the art to the methods taught by Liu et al. Wills et al. and Bramwell. Thus, there is clear motivation to combine.

Art Unit: 1632

(ii) Cajot, Katayose, Srivastava, Wills, Liu, Zhang and Bramwell

Claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cajot et al. taken with Wills et al. or Liu et al., in view of Zhang et al. or Bramwell.

(a) Katayose and Srivastava

The prior rejection of claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 under 35 USC § 103 as being obvious over Katayose et al. or Srivastava et al. is withdrawn in view of appellants filing of a Declaration under 37 CFR § 1.131 on November 16, 1999, paper # 25. Appellants arguments as they apply to the remaining rejection of Claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 as being unpatentable over Cajot et al. taken with Wills et al. or Liu et al., in view of Zhang et al. or Bramwell are addressed.

(b) Extrapolating from *In Vitro* to *In Vivo*

At page 17 of the Brief, appellants argue that extrapolating from *in vitro* to *in vivo* is problematic and unpredictable. There has been no rejection on the record that extrapolating from

Art Unit: 1632

in vitro to *in vivo* inhibition of tumor cells expressing p53 is problematic or unpredictable. Such extrapolation depends on the facts of each particular case and the evidence provided in the prior art. In the instant case, Wills et al. establishes that inhibition results achieved from *in vitro* transfection of cancer cells with adenoviral vectors encoding p53 is predictable of *in vivo* inhibition of cancer cells transfected with adenoviral vectors encoding p53 (see figures 4-7, which demonstrate that both Saos-2 and H69 tumors had inhibition *in vitro* and *in vivo*). Liu et al. further confirms that *in vitro* inhibition growth assays were predictive of *in vivo* inhibition with squamous cell carcinoma (see whole article, especially abstract). Furthermore, appellants IDS establishes the state of the art with respect to p53 expression and demonstrates an overwhelming consensus in the art that if *in vitro* inhibition was achieved this would be predictive of *in vivo* inhibition with respect to p53 expression in cancer cells.

Appellants point to a teaching in Srivastava that the *in vitro* growth of a single cancer cell line (LnCaP) was not predictive of *in vivo* results (see page 17 of Brief). However, as indicated by Srivastava, this was an unexpected and “intriguing” result. Srivastava (page 847, second column) goes on to state that, in contrast to the results achieved by another investigator, “our study exhibited a potent inhibitory effect on all the metastatic human prostate cancer cell lines tested.... Our preliminary results from intratumoral injections of the AdWTp53 have also shown inhibition of tumor progression of DU145- and PC3-derived tumors in nude mice.” This provides

Art Unit: 1632

further support that the standard in the art was that the *in vitro* results were generally predictive of *in vivo* results in most tumors. Each of Srivastava (page 847) and Cajot et al. (see abstract and page 6958) teach that in some tumors if no *in vitro* inhibition is observed, there can still be inhibition *in vivo*. These references suggest that *in vivo* testing may be necessary to observe the full potential of the expression of p53 in tumor cells. Therefore, it is clear that, if growth inhibition was achieved *in vitro*, then *in vivo* growth inhibition for tumor cells transfected with wild-type p53 was also achieved with a reasonable expectation of success. However, the testing of tumors *in vivo* may achieve inhibition where no inhibition was observed *in vitro* (Cajot et al., abstract and page 6958). These teachings do not teach confusion in the field, but emphasize that *in vivo* testing may be necessary to determine the full potential of the expression of p53 in tumor cells. Appellants have not provided any evidence in the art which suggests that if *in vitro* inhibition is achieved that *in vivo* inhibition would not be achieved. All of the art suggests the opposite, that is- If *in vitro* inhibition is achieved, *in vivo* inhibition is always achieved.

(c) Srivastava and Katayose

The prior rejection of claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-103, 108-132 and 137-145 under 35 USC § 103 as being obvious over Katayose et al. or Srivastava et al. is withdrawn in view of appellants filing of a Declaration under 37 CFR § 1.131 on November 16, 1999, paper # 25. Therefore, this argument is moot.

Art Unit: 1632

(d) Extraneous Prior Art

Appellants argue that other references in the art (other than the references applied in the 35 USC § 103 rejection) must be taken into consideration. Appellants cite Baker et al. (Science, 249: 912, 1990, Exhibit J) and Casey et al. (Oncogene, 6: 1791, Exhibit K) as teaching that *in vitro* attempts to inhibit p53-positive tumors by expressing wild-type p53 in cancer cells did not work.

Contrary to appellant's arguments, neither Baker et al. nor Casey et teach away from the claimed invention. Baker et al. actually teaches towards the claimed invention. At page 914, Baker et al. states:

The transfection and expression results of Table 1 and Fig. 2A suggest that cells at the premalignant stages of tumor progression (VACO 235) may be less sensitive to the inhibitory effects of wild-type p53 than malignant cells (SW480, SW837, and RKO). This hypothesis is consistent with previous results that suggest the wild-type p53 is less inhibitory to the growth of normal rat embryo fibroblasts than to their oncogene-transfected derivatives (8). **This sensitivity may only be relative: expression of the wild-type gene at high concentrations might inhibit the growth of any cell type, including non-neoplastic cells, by overwhelming normal regulatory processes such as phosphorylation (20,21).**

(emphasis added). Thus, Baker actually teaches that overexpression of p53 would inhibit p53 expressing cells and cites three references in the prior art which also support this hypothesis.

Baker et al. further states that p53 expressing cells are "less sensitive to the inhibitory effects of wild-type p53", not that these cells "**failed** to demonstrate suppression" as suggested by appellants (page 19 of Brief). At most, Baker et al. and Casey et al. teach that not all p53 tumors will be inhibited by exogenous expression of p53, but this does not indicate that other tumors

Art Unit: 1632

would not be inhibited by exogenous expression as stated by Baker et al. Appellants claims are not directed toward specific cancer cell embodiments where the expression of exogenous p53 had been shown to not be effective *in vitro*.

Appellants emphasize that the examiner must consider the entirety of the prior art when assessing the obviousness issue. The examiner has done just that. Cajot et al. teaches that p53 positive tumors expressing exogenous p53 are inhibitory *in vitro*. Liu et al. and Wills et al. teach that inhibition achieved *in vitro* is predictive of inhibition *in vivo* with various tumor types. Furthermore, Cajot et al. and Srivastava et al. each teach that even if some tumors do not exhibit inhibitory effects *in vitro*, inhibition *in vivo* may still be achieved (Srivastava et al., page 847; Cajot et al., abstract and page 6958). Baker et al. (a reference not relied upon in the rejection) lends support for the teachings of Cajot et al. and cites three references known in the art which give credence to the fact that overexpression of p53 can result in inhibition of the growth of cells. Zhang et al. and Bramwell suggest combining gene therapy with other cancer treatment regimens to achieve better inhibitory effects. Thus, when the art is viewed in its entirety, there is clear motivation to treat p53 positive tumors with exogenous p53.

(e) The Cajot Studies

Appellants argue that Cajot et al. suffers from additional defects rendering the results achieved by Cajot et al. invalid. Appellants argue that the wild-type p53 shuts down the SV40 promoter and that cells were eliminated in culture due to toxicity rather than p53 inhibitory effects

Art Unit: 1632

on the tumor. Appellants argue that Subler et al. supports the hypothesis that p53 down-regulates the SV40 promoter and that the skilled artisan when viewing Cajot et al. in light of Subler et al. would find the observations of Cajot et al. invalid (page 20 of Brief). Appellant's arguments have been carefully considered, but are not deemed persuasive.

Contrary to appellants argument that Cajot et al. does not indicate that the exogenous p53 detected was mutated. At page 6956, second column Cajot et al. states, "To our knowledge, we are the first to report growth suppression induced by **high level expression of exogenous wild-type p53 in lung cancer cells expressing normal endogenous p53.**" (emphasis added). At page 6957, last paragraph, Cajot et al. indicates that the Hut292DM cells contained endogenous wild-type p53. At page 6959, first column, Cajot et al. indicates that the Hut292DM cells do not contain a p53 mutation and that the "expression of wild-type p53 may lead to the growth arrest of highly proliferative tumor cells expressing endogenous wild-type p53.

Any reliance on Subler et al. by the skilled artisan suggests that the SV40 promoter is the best promoter to use, since Subler et al. states, "[t]he SV40 early promoter seems to be the least affected under our assay conditions." (page 4760, top of second column). Subler et al. indicates that p53 inhibits a wide variety of cellular and viral promoters (page 4760, first column under Discussion). At the paragraph bridging pages 4760-4761, Subler et al. states that p53 can bind to SV40 and can function as an activator as well as an inhibitor. Subler et al. goes on to say that it requires a relatively higher concentration of p53 plasmid to inhibit the SV40 early promoter, than other promoters. Therefore, given the teachings of Subler et al. one of skill in the art would

Art Unit: 1632

recognize the potential of p53 to down regulate all promoters, but would be motivated to use the SV40 early promoter to get the highest level of expression possible. Thus, appellants arguments regarding the teachings of Cajot et al. and Subler et al. are misstated and misconstrued into giving an interpretation that the art does not teach.

Finally, Cajot et al. transplanted the transduced tumors *in vivo* and demonstrated inhibition of these transplanted tumors. Geneticin (the allegedly toxic agent) was not present in the *in vivo* assays.

(f) Evidence of Clinical Data

Appellants argue that the their clinical data supports “surprising and unexpected” results which overcome the rejection under 35 USC § 103. The data discloses treatment of head and neck cancer with intratumoral injections of adenoviral vectors encoding p53. Appellants argue that the data achieved in phase II clinical trials (page 22-23 of Brief) provides better results in p53 adenoviral treatment of p53 positive tumor than p53 negative tumors and that these results were unexpected. However, the calculations of the data leading to the supposed unexpected results is faulty. Appellants are doing a direct comparison statistical calculation on two population groups with different numbers of patients being treated. This is an improper statistical calculation. Therefore, there is no evidence of unexpected results. Even if the statistical calculation were valid, however, appellants claims are not limited to the cancer type leading to the supposed unexpected result.

Art Unit: 1632

It is noted, the examiner has not challenged the enablement of the claimed invention. To the contrary, the examiner finds the invention as claimed fully enabled and obvious.

(iii) Motivation to Combine the references applied under 35 USC § 103

In response to appellant's argument that there is no suggestion to combine the references (Brief at page 23), the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, the references themselves provide the motivation to combine, since Cajot et al., Liu et al. and Wills et al. are all directed to treating tumors with vectors encoding wild-type p53 and Zhang et al. specifically teaches combining p53 gene therapy treatment with other well known cancer treatment methods such as surgery, radiation therapy, chemotherapy and immunotherapy (see pages 1083-1084; page 1085, last paragraph; and page 505 second column). Zhang et al. explicitly directs one of ordinary skill in the art to the methods taught by Liu et al. Wills et al. and Bramwell. Thus, there is clear motivation to combine.

Art Unit: 1632

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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